WAR MEDICINE AND SURGERY

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ANTISEPSIS AND DISINFECTION.

DURING the present war there has been a revival of interest in antiseptics, and the view that they all do more damage to tissues than to bacteria is nowadays challenged. Several factors have contributed to this new outlook: (a) the development of sulphonamide therapy to include local application of the drug, and thereby to bring the sulphonamides into the class usually accepted as antiseptics; (b) the introduction of better methods of applying antiseptics, such as the use of the Bunyan bag and the use of the drug in powdered form; (c) the discovery of the mode of action of sulphonamides and an increase in knowledge about antiseptic action in general; (d) the preparation of penicillin, which is much more active on certain bacteria than sulphonamides, and much less toxic, and suffers only from the disadvantage that it is "probably the most precious substance used in Medicine with the single exception of radium".[9]

There is no simple answer to the question of whether a given substance is a good antiseptic. In any discussion of antiseptics it is important to keep in mind the different conditions which limit their action, and the following four different purposes for which they are used: (a) Chemical sterilization has long had an assured place in the disinfection of suture material, certain surgical instruments, sick room utensils, and various types of non-living matter, which it is impracticable, or inconvenient, or undesirable to sterilize by heat. The value of chemical disinfection is well known, though certain limitations are often overlooked, as when syringes are "sterilized" by being washed out with methylated spirit. (b) For many years attempts have been made by various methods to disinfect the skin prior to surgical operation, and on the whole, the results have always been considered worth while. We now believe that it is probably impossible to sterilize living skin, though a considerable reduction in the number of bacteria present can be readily achieved, and some recent claims regarding complete sterilization await further examination. (c) Antiseptics may be employed to prevent the infection of wounds. Now that sulphonamides have been successfully used for this purpose in various war zones, there can no longer be any doubt about the possibility of prophylaxis against wound infection. (d) Antiseptics are used in the treatment of established infection. This use, of course, imposes the most difficult test that an antiseptic can undergo. Most of the older types have been found wanting when tried therapeutically, and the newer drugs also have strict limitations. An efficient antiseptic must be destructive to microorganisms in a concentration which is harmless to tissues, and all antiseptics must be examined from these two aspects. It is relatively easy to determine whether a chemical can destroy a given microorganism under certain arbitrary conditions, and it is also easy to perform a standardized toxicity test. These tests will exclude certain potential antiseptics from clinical consideration, and they are valuable for this reason, but

a chemical which is rated highly by such examinations may still fail in clinical practice, where many factors may nullify the bactericidal effect and where unsuspected toxicity may become apparent. It is obviously important, however, to make the laboratory tests as thorough as possible. A recent report by the Council on Pharmacy and Chemistry of the American Medical Association sets out three methods of testing germicidal efficiency and one method of testing toxicity, to be used in conjunction with critical clinical evidence in evaluating skin disinfectants.[10]

The history of the use of antiseptics is a warning against too confident an assessment of recent literature on the subject, but the following topics have been selected as covering important advances in the practice of antisepsis: (a) penicillin and other "biological antiseptics"; (b) sulphonamides; (c) acridines; (d) "Zephiran; (e) "Ctab"; (f) "Propamidine"; (g) the disinfection of skin; (h) the disinfection of air; (i) the problem caused by the shortage of surgical rubber gloves; and (j) the preservation of blood and blood derivatives from contamination by micro-organisms.

Penicillin.

Penicillin is produced in small quantities during the growth of the mould *Penicillium notatum*. A yield of one gramme of the purified product from twenty litres of culture fluid would be regarded as exceptionally high, and the drug is therefore difficult to obtain. This problem of itself is not insuperable; it could be overcome by production on a large scale; but such a step introduces other difficulties. The choice of the most productive strain of the mould and of the most suitable culture medium is not easy. The cultures are highly susceptible to contamination by bacteria and other organisms, and the contamination not only affects the growth of the mould, but also tends to destroy any penicillin formed. Finally, even when a good yield has been obtained in the culture medium, there is difficulty in extracting, purifying and stabilizing the product.

On account of these problems in the production of penicillin by biological methods, attempts have been made to synthesize the substance; but synthesis has not yet been achieved, for the molecule is complex and unstable. Several commercial firms are interested in the marketing of penicillin and, using the biological methods, have carried production to the pilot plant stage. Their success seems to offer most hope for an increased supply of penicillin in the future, but the prospect of meeting even urgent military requirements is still remote.

It is obvious from the interest that is being taken in penicillin that the limited amount already used for clinical experiment must have proved promising. A Committee on Medical Research in America has reported on the use of the drug in three hundred patients, some of whom were soldiers with unhealed compound fractures, or osteomyelitis, or wounds with long-established infection. Their conclusions are as follows:[12]

There is good reason for the belief that it (penicillin) is far superior to any of the sulfonamides in the treatment of *Staphylococcus aureus* infections with and without bacteremia, including acute and chronic osteomyelitis, cellulitis, empyema, infected wounds and burns. It is also extremely effective in the treatment of hemolytic streptococcus, pneumococcus and gonococcus infections which are resistant to sulfonamides. It has not been found effective in the treatment of subacute bacterial endocarditis. Studies of the results of its local application are still inadequate.

Properly made preparations have given no toxic reactions, even from the largest dosage. Its rapid excretion in the urine necessitates frequent administration when given intravenously or intramuscularly.

Penicillin should not be given by mouth because it is destroyed by the acid in the stomach. It is best administered intravenously by a continuous drip, though some impure preparations are pyrogenic.

Penicillin is most useful, at present, in the treatment of overwhelming infection, especially that due to *Staphylococcus aureus*, *Streptococcus pyogenes* or *Pneumococcus*. Experimentally it has shown a marked action against *Actinomycosis bovis* and the organisms of gas gangrene. It is not very effective against Gram-negative bacteria or the tubercle bacillus, or any strain of *Streptococcus viridans* other than *Streptococcus salivarius*.

Penicillin has the advantage of not being affected to any appreciable degree by pus or products of tissue autolysis, and of being influenced only to a minor extent by the number of bacteria present. It is therefore active under conditions which annul the bactericidal power that sulphonamides normally possess. Further, penicillin is not affected by the development of resistance towards sulphonamides, and may prove valuable in preventing the spread of these drug-resistant strains through the community.

Other Biological Antiseptics.

Following the successful use of penicillin, a systematic study has been made of fungi, particularly of the genera *Penicillium* and *Aspergillus*, in the hope of finding further antibacterial substances. Many such products have been isolated, though none has yet proved outstandingly successful. Amongst the bacteria present in soil, however, has been found a sporing, Gram-positive, aerobic bacillus, probably *Bacillus brevis*, an extract of which has proved highly destructive to staphylococci, streptococci and pneumococci. The crude extract is tyrothricin, and it can be divided into two active constituents: gramicidin, which makes up 15% of the whole, and tyrocidin. Gramicidin is the more powerful and less toxic of the two components, and, although it acts only on Gram-positive bacteria, it is the more favoured preparation.

Gramicidin is too toxic for any method of use other than local application. The few clinical reports so far published on its use by local administration are favourable.

Sulphonamides.

Various sulphonamides have been used for local chemotherapy. Sulphanilamide has the advantage of being relatively soluble, so that it quickly reaches a high concentration, and readily diffuses into inaccessible parts of the wound. It persists as crystals for such a short time that it does not provoke a foreign body reaction. It is probably the most popular drug for local application, but it has the disadvantages of being rapidly absorbed, and of being relatively ineffective against such common organisms as staphylococci and the gas gangrene group. Sulphathiazole or sulphadiazine, if available, may be used instead, for these drugs are absorbed less quickly and are active against a wider range of bacteria. They are liable to provoke a foreign body reaction, however, and they diffuse slowly into the recesses of a wound; moreover, their greater bacteriostatic power is partly offset by their lesser solubility. Sulphathiazole is, weight for weight, the more active of the two, but also the more toxic. By mixing sulphanilamide with the less soluble sulphathiazole or sulphadiazine, a preparation is obtained which includes the virtues, but also the vices, of both types of compound.

The drugs are prepared in the form of microcrystals of such a size that they are readily soluble and have little tendency to cake in the wound. Interest has been roused in the sterilization of sulphonamide crystals by the occurrence of a case of tetanus, which was possibly due to organisms present in the sulphonamide used on the patient. An investigation of commercial sulphonamide crystals showed that they were rarely sterile; and, though they seem to be reasonably safe in practice, it is obviously best to put the question beyond doubt by using a sterile product. Manufacturers are now issuing such a product, but meanwhile the stock already on the market should be sterilized by the user before he employs it for local treatment. This can be done in the case of sulphanilamide by using dry heat, obtained by means of a paraffin bath or an electric oven, to maintain the crystals at 150° C. for one hour. Autoclaving is also feasible if carried out with certain precautions to prevent caking.[33] Sulphathiazole can be sterilized by the paraffin bath method.

Sulphonamides are applied locally both in the prophylaxis and in the treatment of infection. The results in the former case are good enough to make the drug a valuable ally, but there is no justification for what has been called "a trend towards an ignorant complacency" on the part of surgeons.[16] In the treatment of established infection by the local use of sulphonamide there are several difficulties: pus inactivates the drug and so must be removed regularly by irrigation; sulphonamides are not effective when the number of organisms present is large; and, finally, some bacteria are resistant; for example, even sulphathiazole is not markedly active against staphylococci.

In using sulphonamide prophylactically as a first-aid dressing, crystals are sprinkled throughout the wound and the question of dosage is not important. When the wound is excised, the dose is restricted to 0·1 gramme per square inch of wound, an amount which is enough to provide a heavy frosting. There is a tendency to sprinkle wounds haphazardly with sulphonamide; Long recommends that not more than ten grammes of sulphanilamide should be given by local application to any one patient in twenty-four hours.[30]

There is no marked toxic action from even a saturated solution of sulphonamide on the tissues of the wound, except, possibly, that exposed nerve trunks may be damaged. Some cases have been reported in which absorption of the drug was sufficient to cause general toxic effects, and this is an especial danger in the treatment of burns.

Acridines.

Acriflavine is well known to surgeons of the Great War, and in spite of certain advantages, such as the ability to act in the presence of proteins, its reputation at the present day is not high. Although it is conceded to be one of the best of the older antiseptics, it has suffered from the general criticism made against the antiseptic treatment of wounds, namely, that the damage done to the bacteria is more than counter-balanced by the damage to the tissues. The related compounds euflavine and "Rivanol" have shared its fate.

In recent years, however, it has been pointed out that proflavine is as effective as acriflavine and much less toxic.[6] The preference shown for acriflavine in the past was due largely to its solubility, which made the preparation of concentrated stock solutions an easy matter. Acriflavine is actually a mixture of substances made from proflavine, and varying somewhat in composition. It is therefore more expensive than proflavine as well as more toxic and less reliable. When these facts become more widely known acriflavine will take its place as a superseded drug.

Proflavine is known to be active against most pyogenic organisms with the exception of *Proteus* and possibly *Pseudomonas*. It is particularly valuable in dealing with the staphylococcus, which is resistant to antiseptics. The most striking therapeutic results reported so far from the use of proflavine are those of Mitchell and Buttle.[11] These workers used proflavine sulphate as a powder—a form in which the sulphonamides have been successfully

employed. An amount varying from 0·5 gramme to 2·0 grammes was sprinkled onto the wound or, if necessary, introduced by a blunt dissector. The patients were battle casualties from Libya; many of them had intractable infection which had been unsuccessfully treated by sulphonamides. The results with proflavine were often dramatic; in only six of the 80 patients was the treatment ineffective, and in only one was there any suggestion that healing had been delayed by the treatment. There were no general toxic effects from the drug, though a few patients complained of a slight burning sensation when the powder was applied. These excellent results require confirmation.

Proflavine bisulphate, the official preparation, gives an acid and slightly irritating solution. The monohydrochloride gives a neutral solution, but is not available commercially, and Dr. A. Albert, of Sydney, has suggested that the bisulphate serves just as well if it is neutralized by sodium carbonate.

Proflavine has the structure 2:8-diaminoacridine. The related compounds, 2:7-diaminoacridine and 5-aminoacridine, also seem to be effective antiseptics. The former has a very low toxicity and can be used on cerebral tissue without causing fibrosis; the latter does not stain the skin and is the only member of the group which is so stable to light that it need not be dispensed in a brown bottle. Full clinical reports on the use of these two drugs have not yet been published.

"Zephiran."

"Zephiran" is a mixture of quaternary ammonium compounds having a high molecular weight. Coconut oil is used in its preparation, the fatty acids of the oil providing alkyl radicals. The solution of "Zephiran" is detergent and the solute ionizes to form a complex cation, so that "Zephiran" is commonly referred to as a cationic detergent. It penetrates and wets surfaces very well, and destroys bacteria, apparently by the union of the cation with acidic groups on the bacteria to form feebly ionized compounds.[1]

"Zephiran" has come into prominence recently as a suitable disinfectant for hospitals, which possess only restricted supplies of the mercuric chloride, phenol and cresol on which they formerly relied.[5] "Zephiran" concentrate is available in Australia as a 10% solution of the solid. The following concentrations have been recommended: (a) in the sterilization of instruments, use a 1 in 50 dilution of the 10% concentrate for ten minutes; (b) in the sterilization of the hands use a 1 in 200 dilution of the 10% concentrate for half a minute.

There are two important provisos concerning the use of "Zephiran" as a disinfectant:[5] (a) the presence of organic matter interferes with its action, so that pus, blood and such like must be removed from instruments before the sterilization; and (b) soap strongly inhibits the action of "Zephiran", as could be predicted from chemical principles. Therefore any soap used to clean the hands or instruments, prior to the disinfection, must be very thoroughly removed.

"Zephiran" is relatively non-irritating to the skin when used as a disinfectant in effective concentrations. It is even said to be emollient.

"Ctab."

"Ctab", like "Zephiran", is a synthetic cationic detergent. It is used as a 1% solution which is clear and has a slight fishy odour. It cleans and sterilizes and has similar uses and limitations to "Zephiran".

"Propamidine."

"Propamidine" is an aromatic diamidine which has been used in 0·1% concentration, made up in a water-soluble jelly base. The results so far in the treatment of pyogenic infection are encouraging.

The Disinfection of Skin.

The bacteria found on human skin can be divided into two classes: "resident" organisms and "transient" organisms.[6] The resident organisms can be reduced in number by washing the skin or by using antiseptics, but they cannot be eliminated, presumably because they are hidden deeply in the layers of the skin or protected in some other way. The "transient" organisms consist of species which are not usually found on the skin and which can be removed from it by washing, or by the use of antiseptics. Streptococcus pyogenes, which is of special importance in connexion with puerperal and surgical sepsis, belongs to this class; and so do Pseudomonas pyocyanea, Proteus vulgaris and probably also Corynebacterium diphtheriæ; it is difficult to place Staphylococcus aureus in the appropriate classification, but, if not resident, it is a frequent contaminant. Amongst the resident organisms are staphylococci, sarcinæ, non-hæmolytic streptococci, diphtheroids, and some aerobic spore-bearing types.

The most important part of the toilet of the skin for surgical purposes is an initial thorough washing with soap and water, carried out with the help of a nail brush. This removes the transient flora and reduces the resident flora; in addition it cleans away grease and protein films which would hinder the action of the antiseptic used subsequently. Household bar soap has a better bactericidal effect than refined toilet soaps; its action is, of course, most marked when the volume of water used is small, so that the practice of washing under a tap is not as good as that of using three or four pints of water.

The antiseptic of choice for use on the hands is a solution of chloroxylenol. "Dettol" is an efficient proprietary preparation of this substance, but it must be used undiluted. The hands are kept in the antiseptic solution for two minutes and then, to avoid irritating the skin, they are dried before gloves are put on. A bactericidal film remains on the skin and is effective for several hours.

When the skin of a patient is being prepared prior to operation, iodine, in the form of a 2% aqueous solution containing also 2% of sodium iodide, may be used in preference to "Dettol". Iodine is probably more efficient, but its use involves a small risk of idiosyncrasy. Chloramine T is also effective, but has an unpleasant smell and is somewhat unstable. Whichever drug is used, the time of application must not be less than three minutes. The following antiseptics are ineffective when used on the skin for three minutes only: alcohol, in a solution of 75% by weight; perchloride of mercury, 1 in 1,000; and "Merthiolate", 1 in 1,000.

The Disinfection of Air.

Interest has been stimulated in the problem of the disinfection of air by overcrowding in air-raid shelters and by the desirability of limiting contamination in laboratory rooms where sterile products are being packed. Two main methods have been suggested: chemical disinfection and the use of ultra-violet light.

Several chemicals such as propylene glycol, resorcinol, hexyl resorcinol, and hypochlorites have proved effective. One method that is commended by its simplicity is the use of 1·3% bleaching powder solution or 1·0% sodium hypochlorite solution, sprayed into the atmosphere by means of a flit gun.[6] The spraying has to be repeated every twenty or thirty minutes, and is continued until the odour of the hypochlorite is perceptible. A volume of about 20 cubic centimetres of solution was sufficient, in the original experiments, for a room of 1,600 cubic feet capacity. The chemical is not effective unless the relative humidity is fairly high—somewhat over 70%. The reduction in total bacterial content is of the order of 33%, but the reduction in the content of pathogens is probably greater.

Hypochlorites are easily obtained and inexpensive, so that the method is simple, cheap and reasonably efficient. Almost all the subjects of Challinor's experiments agree that the hypochlorites have a "freshening" effect on the air of the room, and a marked deodorizing action.

It is now certain that ultra-violet light of wave-length from 2,500 to 3,000 Ångström units will rapidly kill moist air-borne bacteria. Dried organisms or moulds, however,

are much more resistant and the ultra-violet radiation will kill them only when used in considerable intensity or for long periods. The radiation may be conveniently obtained from a low-pressure mercury-vapour lamp.

The Shortage of Rubber Gloves.

For many years rubber gloves have been regarded as an essential part of a surgeon's equipment. There is no reason to criticize this practice, but, today, gloves are in short supply, and plans have to be made to use material to the best advantage. The following recommendations have been made by the War Wounds Committee of the Medical Research Council: [7]

1. That rubber gloves should be used by all surgeons for operations on septic wounds, and for all operations by surgeons who are carriers of virulent staphylococci.

2. That surgeons who propose to operate without rubber gloves should have their hands tested periodically, to make sure that they do not become carriers of virulent organisms.

3. That fabric gloves are undesirable.

4. That surgeons proposing to operate without gloves should endeavour to maintain a "no-touch" technique as far as possible.

5. That the use of one pair of gloves for several operations is undesirable, even when the gloves are washed in antiseptic from time to time, owing to the risk of unnoticed glove punctures in septic cases. (The frequency of puncture is higher than is generally suspected; it amounts to about 20%. This is a very important consideration, for it is recognized that heat sterilization is the most critical factor influencing the life of gloves, and some hospitals have begun to adopt chemical methods of sterilizing the gloves on the surgeon's hands, and so avoiding both the use of a further pair and the damage of heat sterilization.)

6. That the use of rubber gloves by the theatre sister could in many cases be obviated: (a) if forceps are used to pass instruments to the surgeon; (b) if the surgeon or the "first assistant" picks up the instruments, and either lays them on a special towel after use, or returns them direct to a sterilizer; (c) if the needles likely to be needed for an operation are threaded by means of forceps or, alternatively, are threaded before they are sterilized.

7. That the use of rubber gloves for surgical dressings is generally unnecessary except in the case of procedures which are too complicated to be managed with forceps alone.

Preservatives for Stored Blood and Blood Derivatives.

It is well known that infection of blood is not a troublesome problem if the blood is drawn from a donor and given at once to a patient. The safety of the usual blood transfusion in this respect, however, depends not on the absence of contaminants from the transfused blood, but on their lack of opportunity to multiply. If blood is stored, opportunities for multiplication become greater; some samples are likely to be infected even when refrigeration has been satisfactory; the danger is much greater when, for some reason, the blood is allowed to stand for more than a few hours at room temperature.

It is therefore desirable to use a preservative in stored blood. Many have been suggested, but the various sulphonamides have probably proved the most satisfactory.

For the preservation of serum or plasma the organic mercurials such as "Merthiolate" or phenyl mercuric nitrate are often used. These substances have very good bacteriostatic powers, but are much less efficient as bactericides. It should be realized that the protection given by preservatives in blood or blood derivatives is only

relative; an occasional resistant organism may multiply in their presence and their use should not induce complacency.

Mode of Action of Antiseptics.

During the last three years the mode of action of sulphonamides has been satisfactorily explained. These drugs divert to themselves an enzyme system which normally deals with a closely related substance, p-aminobenzoic acid. This acid is essential for the metabolism of certain bacteria, and a diversion of the appropriate enzyme system from it is therefore lethal to the organisms. This theory may be capable of a wider application. Thus if a substance is known to be essential for bacterial metabolism it may be possible to find closely related substances which are similar enough to divert the bacterial enzymes, but sufficiently different to be unable to produce the specific effect of the metabolite on bacterial growth. The related substance might then be expected to act as an antiseptic. Work based on such a theory has already proved profitable.

A recent contribution to the theory of antiseptic action stresses the importance of some well-known physical and chemical properties in explaining the mode of action. [1] This method of attack has been neglected in the past, and it has often been assumed that it was too difficult for profitable study. A wave of rationalism has been caused by the work on sulphonamides, however, and, under the stimulus of the wartime demand for better methods of preventing and treating infection, useful advances in the theory of antiseptic action are being made. The results should be seen in a more intelligent use of these drugs.

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